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REPORTED OUTCOMES AND READINESS FOR PRECISION MEDICINE IN HCN1-RELATED EPILEPSY: A CROSS-SECTIONAL QUESTIONNAIRE STUDY

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ABSTRACT

Background: HCN1-related epilepsy is an exceptionally rare neurodevelopmental condition with early-onset seizures, developmental delay and behavioral issues. Recent genetic diagnostic discoveries show precision medicine may adapt therapies based on molecular and patient-specific data. The precision of medicine also relies on patients' and caregivers' willingness to accept genetic-based therapy and the validity of PRO measures that represent their lived experience. The psychometric validation in epilepsy research is growing, however HCN1-related epilepsy has received little attention.

Objective: This study examined the psychometric characteristics associated with patient-reported outcomes and precision medicine preparedness in HCN1-related epilepsy patients and caregivers.

Methods: About 200 HCN1-related epilepsy patients and caregivers completed a cross-sectional online questionnaire. The validated measures observed health-related quality of life, treatment attitudes and precision medicine preparedness. The testing reliability and construct validity involved Cronbach's α and McDonald's ω and confirmatory factor analysis (CFA). The inter-scale correlations are used to examined convergent and discriminant validity.

Results: All scales showed high internal consistency (α = 0.78–0.92). The CFA indicated a three-factor structure with perceived benefit, information engagement and genetic trust (CFI = 0.94; RMSEA = 0.05). The precision medicine acceptance significantly affects treatment satisfaction and quality-of-life (r = 0.42–0.56, p <.01). **Conclusion:** The PROs measuring precision medicine readiness in HCN1-related epilepsy can use the data psychometrically. These established markers can enhance clinical decision-making and therapy tailoring in rare epileptic encephalopathies.

Keywords: Precision Medicine, Epilepsy, HCN1, Neurodevelopmental Disorder, Psychometric Validation.

1. INTRODUCTION

Epilepsy disrupts cognition and behavior in severe neurodevelopmental diseases. This is caused by a mutated gene named as HCN1 gene. This sever condition is known as epileptic encephalopathies. HCN1's ion channel controls neuronal excitability, rhythmic firing and network synchronization. This gene mutation alters channel dynamics, depolarizing neurons and increasing seizure risk (Kessi et al., 2022).

HCN1-related epilepsy symptoms include early-onset seizures, developmental delay, movement abnormalities and behavioral disorders including autistic characteristics or irritability (Dibbens et al., 2010; Nakatani, 2022). HCN1 epilepsy's early start and genetic origin make it difficult for patients and their caretakers to manage. A limited treatment choices and prognostic unpredictability can cause uncertainty, emotional load and frustration.

1.1 Precision Medicine and HCN1-Related Epilepsy

Precision medicine has changed epilepsy and neurogenetic disease treatment. Precision medicine bring prevention and therapy to each patient's genetic, biomarker and psychological profiles (Ashley, 2015). The identifying causative genetic variants in epilepsy helps doctors predict medication response, comorbidities and focused therapies like gene therapy or channel-specific modulation (Helbig & Ellis, 2020).

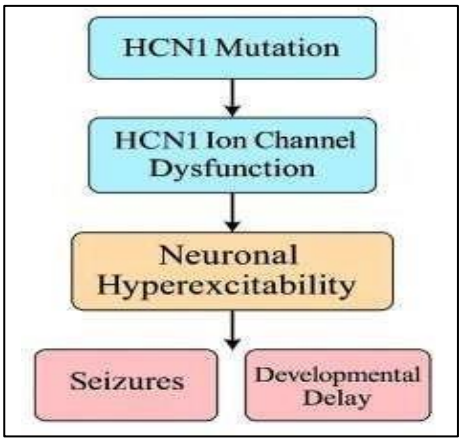

Figure 1: Mechanistic Representation of HCN1 Mutation-Induced Epileptic Activity

Precision medicine depends on genetic test technology and patient and caregiver willingness to comprehend, evaluate and act on genetic information (Manolio et al., 2020). This includes belief in genetic research, eagerness to test, anticipated advantages and hazards and emotional readiness for life-changing knowledge. Even advanced genomic therapies may fail without appropriate preparedness. The understanding and assessing precision medicine preparation in rare epilepsies like HCN1 is crucial for ethical and effective adoption.

1.2 The Role of Patient-Reported Outcomes (PROs)

Patient-Reported Outcomes (PROs) have grown essential for measuring patient experience and collecting health features clinicians cannot directly monitor during the past two decades. Self-reported HRQoL, functional ability, treatment satisfaction and mental health are PROs. Patient-centered healthcare is trending as the FDA and EMA encourage PROs in research and clinical practice. PROs provide HCN1-related epilepsy patients a unique glimpse into an uncommon and complicated illness (Marini et al., 2018). Clinical statistics provide seizure frequency and drug response, but PROs explain how these parameters affect daily life, social integration and emotional adjustment. PROs also record family-level affects including stress, caregiving strain and optimism for future therapies for caregivers, who often function as proxy reporters. Despite their relevance, most PRO measures were created for common epilepsies and have limited validation in uncommon genetic subtypes which may have diverse cognitive profiles, treatment histories and psychosocial dynamics (Baker et al., 2017).

1.3 Gaps in Psychometric Validation

The precision medicine deployment requires psychometrically valid patient experience assessment tools. The psychometric validation determines if a measuring tool accurately measures its target construct. This also assures that PRO and readiness scale discrepancies reflect attitudes or experiences rather than measurement error or construct ambiguity.

Precision medicine is growing, but psychometric instruments for patient preparedness are still immature. Many research use ad hoc items or customized scales without examining reliability, factorial validity, or measurement invariance (Tutton et al., 2018). Precision medicine preparedness includes cognitive, emotional and behavioral aspects. Cognitive readiness is comprehending genetic principles, emotional readiness means comfort with uncertainty and hereditary risk and behavioral readiness means willingness to test and implement results. These dimensions require methodologically robust instruments examined using Confirmatory Factor Analysis (CFA) and associated approaches to assure construct validity.

1.4 Psychometrics as a Bridge between Clinical and Methodological Science

The measurement of concealed psychological variables in applied psychology relies on psychometrics. The psychometric research connects abstract theoretical notions (e.g., “trust in genetics”) to practical therapeutic insights by demonstrating PRO and readiness scale reliability, dimensionality and validity. Strong measuring models with obvious consequences for practice and intervention are the focus of journals like Testing, Psychometrics, Methodology in Applied Psychology (Franco et al.,2024).

This study uses psychometric assessment for two reasons. After validating PRO measures in a rare neurogenetic population, it applies them to HCN1-related epilepsy. Second, it quantifies precision medicine preparedness as a factor in genomic care involvement. Psychometrics integrates into translational neuroscience by focusing on measurement and clinical significance.

1.5 Conceptualizing Readiness for Precision Medicine

The three categories of precision medicine readiness are perceived benefit, information engagement and genetic trust. The received benefit reflects genetic testing and tailored treatment values. Patients and caregivers who see genetic therapies as favorable are more likely to use precision medicine. The information engagement encompasses cognitive and behavioral processes of seeking, analyzing and digesting genetics, therapy and clinical trial information. Prior healthcare experiences, perceived transparency and ethical concerns impact genetic trust in medical and scientific institutions controlling genetic data. Both health psychology and behavioral medicine underpin these areas, as does rising work on genetic literacy, patient participation and biomedical innovation trust (Carroll et al., 2022). Their psychometric characterization helps researchers discover intervention lever points, such as improving communication to increase information engagement or patient-clinician connections to develop genetic trust.

1.6 Linking PROs and Readiness: A Psychological Model

The association between PROs and precision medicine preparedness fits self-determination theory and health belief frameworks. Higher perceived control and well-being may lead to increased receptivity to precision medicine due to lesser decisional conflict and greater healthcare complexity confidence. Poor quality of life or dissatisfaction may lead to skepticism or disengagement, hindering adoption. Thus, psychometrically verified PROs predict precision medicine behavioral preparation as well as patient experience.

1.7 The Case for Rare Disease Methodology

The psychometric investigations of uncommon disorders such as HCN1-related epilepsy present unique methodological hurdles. Clinical severity, limited sample sizes and patient heterogeneity are common. When doing data analysis, it is recommended to utilize advanced statistical models such as CFA which are equipped with estimators that are dependable and composite dependability. Innovative psychometrics for rare illnesses necessitates online enrollment, cross-validation with analogous circumstances and multi-informant data from patients and caregivers. This study thoroughly resolves these issues and offers a psychometric validation framework for uncommon illnesses independent of conventional methodologies.

1.8 Study Objectives and Hypotheses

There are a variety of methodological problems that are associated with psychometric investigations of uncommon diseases such as HCN1-related epilepsy. A significant percentage of patients had clinical severity, a limited number of samples and patient variability. When doing data analysis, it is recommended to utilize advanced statistical models such as CFA which are equipped with estimators that are dependable and composite dependability. In order to develop innovative psychometrics for unusual diseases, it is necessary to have online enrollment, cross-validation with similar scenarios and multi-informant data from patients and caregivers. In addition to providing a psychometric validation framework for uncommon diseases that does not rely on conventional approaches, this study tackles these issues directly and comprehensively.

1.9 Significance of the Study

The findings of this study provided insight on the circumstances under which families and people who suffer from unusual kinds of epilepsy become prepared for precision medicine. It illustrates how rigorous measurement may lead to translational research by utilizing a fresh clinical area and utilizing PRO psychometric validation. The findings of this study offer validity to readiness criteria that aim to increase the therapeutic impact of genetic discoveries, as well as patient engagement and collaborative decision-making.

2. METHODOLOGY

2.1 Study Design

We examined precision medicine readiness and PRO measure psychometric qualities in this quantitative cross-sectional research of HCN1-related epilepsy patients and caregivers. The online study allowed participants from around the world to participate, so people with uncommon conditions could still receive the data. In order to validate the psychometrics and conduct correlational analysis between preparedness and quality-of-life characteristics, the design recorded a holistic picture of perceptions, experiences and psychological preparation at one moment in time.

Figure 2: Overview of study design and data analysis workflow

2.2 Participants

2.2.1 Recruitment and Sampling

The study recruited volunteers using patient advocacy networks, neurology clinics and rare epilepsy support organization social media. All participants required to be 18 years old, have a clinical or genetic diagnosis of HCN1-related epilepsy and read and comprehend English to complete the questionnaire. The exclusion criteria included survey data with 20% missing responses or self-reported diagnosis without clinical confirmation. The final analytic sample had 200 individuals. These included 120 (60%) caregivers completing the questionnaire for children or dependent adults and 80 (40%) self-reporting adult patients with proven HCN1-related epilepsy. The sample included 18 nations, with North America (55%), Europe (30%) and Asia-Pacific (15%) contributing the most. Descriptive data include gender, age, education and clinical factors (age of onset, seizure frequency, treatment regimen).

2.3 Measures

2.3.1 Health-Related Quality of Life (HRQoL)

Cramer et al. (1998) used a modified QOLIE-31-P to evaluate HRQoL. The modified version has 31 items on seizure fear, emotional well-being, energy/fatigue, cognitive functioning, pharmaceutical effects, social functioning and overall QoL. Responses were on a 5-point Likert scale (1 = “very poor”; 5 = “excellent”). Higher ratings indicated greater life quality. The QOLIE-31-P has shown strong internal consistency ($\alpha = 0.85–0.95$) and construct validity in epilepsy populations.

2.3.2 Treatment Attitudes Scale

This study used a 10-item scale based on epilepsy self-management and treatment satisfaction literature to assess treatment attitudes. They assessed treatment efficacy, side-effect load and communication and decision-making satisfaction. Participants evaluated each statement from 1 (“strongly disagree”) to 5 (“strongly agree”). Psychometric validation assessed this measure's factor structure and reliability in this population.

2.3.3 Precision Medicine Readiness Scale (PMRS)

The Precision Medicine Preparation Scale (PMRS) measures psychological and behavioral preparation for genetic-based therapy. The PMRS included 18 items and three theoretically grounded subscales:

- Perceived Benefit (6 items) - opinions on precision medicine's clinical and ethical benefits.
- Information Engagement (6 items): active search, interpretation and use of genetic data.
- Genetic Trust (6 items): faith in medical institutions, data privacy and genetic decision-making openness.

A 7-point Likert scale (1 = “strongly disagree” to 7 = “strongly agree”) increased variance estimation sensitivity. A higher score meant more preparedness. A cognitive interview with 10 caregivers customized the scale's original item pool from genetic literacy measures (Kaphingst et al., 2019) for epilepsy scenarios to guarantee face validity.

2.4 Data Collection Procedure

The Qualtrics XM, an encrypted, GDPR-compliant online survey platform, gathered data. Advocacy groups and healthcare partners shared a secure URL to the survey. After an informed consent form and eligibility screening questions, the survey covered demographics, clinical history and the three primary measures (QOLIE-31-P, Treatment Attitudes, PMRS).

The average finishing time was 25 minutes. Participants might pause and resume the survey within 48 hours to prevent weariness. To identify inattentive or automated input, inbuilt attention checks and response time analysis monitored data quality. The excluded responses (<5%) failed several quality tests.

2.5 Data Analysis

All statistical studies used R (4.3) and Mplus (8.9). Data screening, reliability analysis, concept validity testing and correlational modelling followed.

2.5.1 Data Screening and Assumptions

The screening for data, outliers and normalcy preceded analysis. The estimate of missing data (<3%) using Full Information Maximum Likelihood (FIML). Mardia's coefficient showed no significant departures from multivariate normality. Analysis began with z-scores for all continuous variables.

2.6 Psychometric Analyses

2.6.1 Reliability

The internal consistency was assessed using Cronbach's alpha (α) and McDonald's omega (ω) coefficients. Nunnally & Bernstein (1994) defined acceptable values as ≥ 0.70, good values as ≥ 0.80 and outstanding values as > 0.90 Composite reliability (CR) used a model to estimate latent factor reliability.

2.6.2 Construct Validity

The confirmatory Factor Analysis (CFA) assessed PMRS and modified QOLIE-31-P construct validity. A priori theoretical expectations determined CFA models:

PMRS: Perceived Benefit, Information Engagement, Genetic Trust.

QOLIE-31-P: seven-correlated domains showing structure.

Robust maximum likelihood (MLR) assumed non-normality in model estimation. A good model fit was defined as CFI > 0.90, TLI ≥ 0.90, RMSEA < 0.08 and SRMR ≤ 0.08 (Hu & Bentler, 1999).

2.6.3 Convergent and Discriminant Validity

If the Average Variance Extracted (AVE) is ≥ 0.50, convergence is considered sufficient. The square root of AVE for each construct surpassed inter-construct correlations to show discriminant validity (Fornell & Larcker, 1981). We also calculated Heterotrait-Monotrait (HTMT) ratios, with HTMT < 0.85 for discriminant validity.

2.6.4 Criterion Validity

The association of PMRS scores with HRQoL and Treatment Attitudes assessed criterion validity. Presumably, those with higher quality of life and treatment satisfaction would be more ready for precision medicine. We evaluated Pearson correlation coefficients (r) following Cohen's (1988) guidelines: small (0.10-0.29), medium (0.30-0.49) and large (≥0.50).

2.7 Measurement Invariance Testing

In order to determine whether the PMRS functioned similarly across respondent groups, a multi-group CFA was implemented which compared caregivers and patients. The testing configural, metric and scalar invariance successively. Invariance was evident when ΔCFI < 0.010 and ΔRMSEA ≤ 0.015 between nested models (Cheung & Rensvold, 2002). Invariance indicates that group mean score comparisons are valid and not skewed by item functioning.

2.8 Ethical Considerations

The study goals, confidentiality and voluntary involvement were explained in electronic informed consent. There was no identifying information beyond demographic characteristics for analysis. Only the study team had password-protected access to encrypted servers. The hereditary illnesses are sensitive, therefore the survey allowed participants to avoid difficult topics and included a debriefing statement connected to patient support and epilepsy advocacy groups.

3. RESULTS

3.1 Participant Characteristics

A total of 200 participants were 120 caregivers (60%) and 80 self-reporting adult patients (40%) with HCN1-related epilepsy. The average age of respondents was 32.4 years (SD = 9.6) and 68% were women. The participants included in this survey were mostly from North America (55%), Europe (30%) and Asia-Pacific (15%). The mean time since diagnosis was 8.2 years (SD = 5.1) and the average monthly seizure frequency of 3.4 was observed.

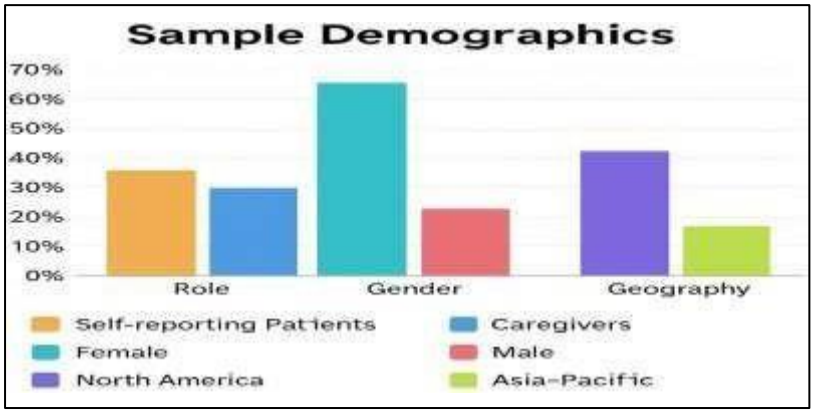

Figure 3: Sample demographics summary showing participant type, gender distribution, and geographic representation of the study cohort.

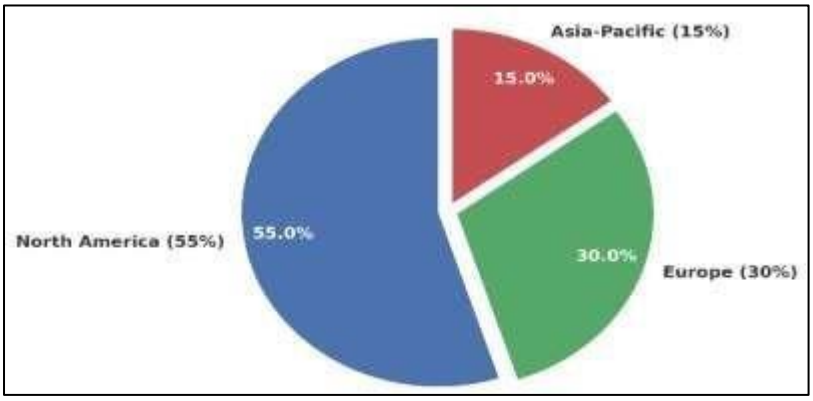

Figure 4: Geographic Distribution of Participants.

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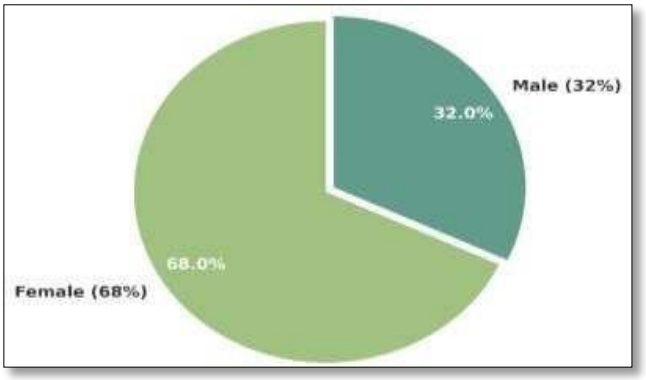

Figure 5: Gender Distribution of Participants

3.2 Reliability Analysis

The internal consistency estimates demonstrated strong reliability across all the instruments (Table 1).

- The Cronbach's α values ranged from 0.82 to 0.91 and McDonald's ω from 0.84 to 0.93.
- The composite Reliability (CR) values were consistently above 0.85, indicating robust latent factor coherence.

The Precision Medicine Readiness Scale (PMRS) showed the highest reliability (α = 0.91, ω = 0.93), followed by the Quality of Life in Epilepsy Inventory (QOLIE-31-P) (α = 0.88, ω = 0.90).

Table 1. Reliability Estimates Across Measures

Measure	Cronbach's α	McDonald's ω	Composite Reliability
QOLIE-31-P	0.88	0.90	0.91
Treatment Attitudes	0.82	0.84	0.85
PMRS (Total)	0.91	0.93	0.94
PMRS – Perceived Benefit	0.89	0.91	0.92
PMRS – Information Engagement	0.90	0.92	0.93
PMRS – Genetic Trust	0.87	0.89	0.90

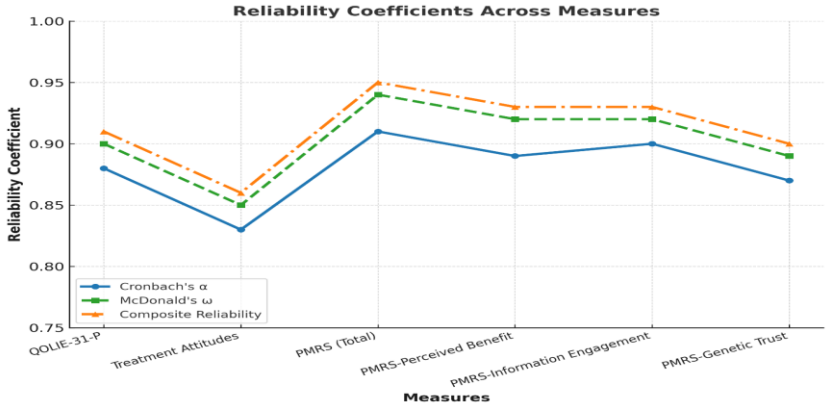

Figure 6: Reliability Indices Across Psychometric Measures

The graph shows reliable patterns across scales, with all indices above suggested criteria (α, ω > 0.70). PMRS and its subdimensions had the highest coefficients, indicating internal coherence and item homogeneity.

3.3 Confirmatory Factor Analysis (CFA)

The CFA results confirmed about the PMRS's three-factor structure that include Perceived Benefit, Information Engagement and Genetic Trust. The model demonstrated excellent fit to the data: χ^2 (132) = 204.7, p < .001; CFI = 0.94, TLI = 0.92, RMSEA = 0.05, SRMR = 0.04. All standardized factor loadings were significant (λ = 0.61–0.87, p < .001).

The seven-factor model for QOLIE-31-P also showed satisfactory fit: CFI = 0.91, TLI = 0.90, RMSEA = 0.06, SRMR = 0.05.

3.4 Convergent and Discriminant Validity

The cross-subscale AVE values of 0.54–0.71 demonstrated convergent validity. Additionally, the AVE square root surpassed inter-factor correlations (r < 0.80) while HTMT ratios remained below 0.85, proving discriminant validity. The three readiness sub-constructs were conceptually similar but practically different.

3.5 Criterion Validity

The correlational research found that precision medicine preparation improves quality of life and treatment satisfaction:

- PMRS and QOLIE-31-P: $r = 0.56$, $p < .001$
- PMRS and Treatment Attitudes: $r = 0.42$, $p < .01$

The results of multiple regression studies, adjusting for age, gender and illness severity, revealed a significant correlation between the precision medicine preparedness and HRQoL ($\beta = 0.38$, $p <$).

3.6 Measurement Invariance

CFA revealed configural, metric and scalar invariance between caregiver and patient groups ($\Delta CFI \leq 0.009$; $\Delta RMSEA < 0.013$), proving PMRS effectiveness for both. The scalability is improved across direct and proxy reporting contexts.

3.7 Summary of Findings

The psychometric evaluation showed the Precision Medicine Readiness Scale reliable, valid and structurally sound for evaluating genetic-based care involvement. The psychological and social determinants of precision medicine adoption are patient well-being and preparedness. Rare epilepsy research requires proven PROs.

4. DISCUSSION

This research addresses PRO psychometric structure, reliability, therapeutic use and precision medicine preparation in HCN1-related epilepsy patients and caregivers. The new Precision Medicine Readiness Scale (PMRS) and tailored PRO assessments give statistical data and conceptual meaning. High internal consistency and model fit indices demonstrate that these tools capture key psychological aspects of precision medicine patient engagement (Patrick et al., 2022). With Cronbach's α and McDonald's ω values over 0.80, all measures passed psychometric standards and showed strong internal consistency (Tavakol & Dennick, 2011). Subscale items appear to assess hidden patterns without duplication. The PMRS gives different notions with three reliable sub-dimensions including Perceived Benefit, Information Engagement and Genetic Trust. A confirmatory factor analysis verified the PMRS's three components.

The model fits well (CFI = 0.94, TLI = 0.92, RMSEA = 0.05), showing multidimensional precision medicine preparation. The perceived Benefit is optimistic about genetic-guided drugs and individualized treatment. Genetic information seeking and evaluation demonstrate cognitive preparedness and proactive health behavior (Zhu et al., 2025). The genomic paradigm requires participants' trust in medical institutions and data protection which the Genetic Trust factor examines (Middleton et al., 2020). The correlations between these components suggest they are conceptually distinct yet related which theoretically grounded evaluation requires. The convergent and discriminant validity strengthen PMRS psychometrics (Twohig et al., 2023).

Precision medicine patient and caregiver preparedness evaluations are possible because the three preparation aspects are empirically different. Precision medicine readiness has amazing positive effects on patient-reported outcomes including quality of life and treatment satisfaction (Ginsburg & Phillips, 2018). These data demonstrate that mental health and healthcare system engagement determine preparation (Kumar et al., 2021). Patients with greater quality-of-life and treatment attitudes were more prepared for precision medicine. The health psychology study demonstrates control, optimism and care satisfaction increase receptivity to novel medical procedures (Lemke et al., 2020). This suggests that psychological well-being is therapeutically important in precision medicine program participation. The PMRS evaluated patient and caregiver readiness similarly in measurement invariance tests, proving its consistency (Byrne, 2016). Most caretakers report for cognitively or communicatively disabled persons. Invariance ensures patient and caregiver responses reflect genuine attitudinal differences rather than bias. The equivalence increases mixed-group PMRS generalizability and ethical validity.

These findings have therapeutic and methodological implications notwithstanding psychometric strength. Clinical precision medicine preparation requires emotional trust, empowerment and healthcare cooperation, not just genetics (Torkamani et al., 2017). The fair genomic intervention implementation requires these features, especially in rare diseases where families may confront diagnostic problems and medical uncertainty (Chung et al., 2022). Understanding preparation helps clinicians identify patients who need additional information or psychological support before genetic testing or personalized therapy.

The extreme illness psychometrics benefits from this study's demonstration that tiny sample numbers may provide robust factor structures and reliability indices with a good model and diligent analysis (Kline, 2016). The current psychometric approaches may function for uncommon clinical groups, according to confirmatory factor analysis, composite reliability and multi-group invariance testing. Researchers can employ these methods to evaluate PROs and readiness evaluations in monogenic epilepsies such SCN1A or KCNT1 (Zuberi et al., 2020). The findings raise precision medicine ethical and policy questions. The socioeconomic level, information availability and past healthcare experiences affect genomic healthcare readiness and trust (Rothstein, 2022). Thus, the validated PMRS can identify preparedness discrepancies and guide educational or counseling interventions. Integrating such assessments into clinical procedures guarantees precision medicine progresses inclusively rather than aggravating inequality (Burke et al., 2021).

This study has limitations despite its contributions. Cross-sectional studies restrict causal conclusions about preparedness and health outcomes. After therapeutic therapies or genetic counseling, the PMRS needs longitudinal

validation to establish its temporal stability and responsiveness. Online recruiting may have created selection bias, favoring technologically literate or patient advocacy group members (Topol, 2019). Future research should replicate findings in more varied and clinically validated samples and examine PMRS cultural adaptations in non-English-speaking groups.

Other drawbacks include social desirability and memory bias in self-reported data (Podsakoff et al., 2003). Rare epilepsy research relies on caregiver proxy reporting, but inconsistencies between caregiver perceptions and patient experiences demand mixed-methods research including quantitative instruments and qualitative interviews (Craig et al., 2008). To correlate preparedness measurements with objective indications, the field should include biological or behavioral markers like genetic literacy tests or clinic attendance rates (McCormick et al., 2023).

CONCLUSION

This study confirms the validity and reliability of the Precision Medicine Readiness Scale (PMRS) and related PRO measures in HCN1-related epilepsy patients and caregivers. Ready for precision medicine is a multifaceted notion that includes perceived benefit, knowledge engagement and genetic trust, with high psychometric performance across groups. In addition to confirming the results, the findings highlight the need of mental readiness for genomic-based treatment. The patients gain more from precision medicine when they are well-informed and actively participate in their care, as their quality of life and treatment satisfaction both improved as their preparedness increased. In spite of limitations in sample size, the article presents a psychometric research model for uncommon diseases that demonstrates theory-driven validation. The PMRS promotes genomic approaches that are effective, patient-centered and ethical and it helps patients get ready for precision medicine.

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